The Gain Paradox

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Dennis Bray and I first met in 1991 -- our paths might have crossed earlier, but if so, I have forgotten. Dazed by the complexity of the movement of growth cones, he wanted to wrap his mind (and computer) around a more tractable behavioral system. So he came to talk with me about bacterial chemotaxis. The next thing I knew, he was busy simulating the phosphorylation cascade, reproducing the phenotypes of a large number of mutants (Bray *et al.*, 1993). Over the years, the models developed by his group have become more sophisticated, e.g. (Andrews and Bray, 2004; Le Novère and Shimizu, 2001), and even playful (Bray *et al.*, 2007). In the course of this work, he has had some profound insights. Take what I call the gain paradox. In the 1980s, by stimulating tethered cells with aspartate ejected from iontophoretic pipettes, we found that the gain of the chemotaxis system is prodigious (Segall *et al.*, 1986). It was not obvious where this gain might be coming from, hence the paradox. In 1993, Janine Maddock found that chemoreceptors in *E. coli* form large clusters, predominantly at one cell pole. This led people to wonder whether *E. coli* might have a nose (Parkinson and Blair, 1993). That did not seem right, because diffusion is so efficient on a micron scale that a nose would work equally well whether in front or behind (assuming that molecules sniffed are not absorbed). We found that *E.*

coli swims either end forward (Berg and Turner, 1995), so a nose in front is soon a nose behind, and conversely. If a cluster is not a nose, what then? Inspired, in part, by the speculations of Jean-Pierre Changeux on allosteric interactions of proteins embedded in lipid bilayers (Changeux *et al.*, 1967), Dennis suggested that the missing gain might be supplied by interactions between adjacent receptors in clusters (Bray *et al.*, 1998). This paper was paired with a *News and views* commentary by Barkai and Leibler (1998). This mechanism for heightened sensitivity was fleshed out with the help of Tom Duke and Yu Shi, using theoretical ideas derived from the Ising model for the ordering of magnetic spins (Duke and Bray, 1999; Shi and Duke, 1998). Applying a FRET technique that allowed us to infer receptor kinase activity, Victor Sourjik and I found that most of the gain in the chemotaxis system does, in fact, arise at the front end of the system, i.e., at the level of the receptors and receptor kinase (Sourjik and Berg, 2002). This confirmed Dennis' idea. Dennis introduced our paper with a masterful summary entitled, "Bacterial chemotaxis and the question of gain" (Bray, 2002). The FRET data have proved sufficiently accurate to inspire an impressive series of theoretical papers that extend the allosteric model of Monod, Wyman, and Changeux (1965). For two recent examples, see (Mello and Tu, 2007) and (Hansen *et al.*, 2008). While the theories have become more refined, the kernel of the idea is contained in Dennis' paper of 1998.

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